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(54) Pharmaceutical composition containing slightly water-soluble drug

Ein in Wasser schwerlösliches Arzneimittel enthaltende pharmazeutische Zubereitung
Composition pharmaceutique comportant un médicament peu soluble dans l'eau

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EP-A- 179 583	EP-A- 257 616
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EP 0 448 091 B1

Description

BACKGROUND OF THE INVENTION

5 The present invention relates to orally administrable pharmaceutical compositions containing a slightly water-soluble drug. The pharmaceutical compositions for oral use according to the present invention are based on the characteristic properties of improved absorption from digestive tract into blood and improved stability.

Due to poor absorption of slightly water-soluble drugs, particularly dihydropyridine derivatives and lipoxigenase inhibitors, from digestive tract, there has been a strong demand for the development of pharmaceutical formulations which afford good absorption in clinical applications. In order to improve absorption, addition of an absorbent and improvement of dosage form designs are necessary, and generally employed means of formulation are pulverization of crystals, noncrystallization, addition of surfactants, cyclodextrin inclusion, emulsification, dissolution in polyethylene glycol and vegetable oil. However, none of these affords sufficient absorption from digestive tract.

In addition, dihydropyridine derivatives are specifically unstable to light, and for this reason, they are prepared into light-resistant preparations or colored preparations and stored in light-resistant containers.

Further, EP-A-0 179 583 discloses adsorption of anhydrous compositions comprising a poorly water-soluble drug and a surfactant onto an adsorber. However, said adsorption is not associated with an improvement in stability of an unstable drug.

SUMMARY OF THE INVENTION

In an attempt to solve the aforementioned problems, an object of the present invention is to provide compositions containing a slightly water-soluble dihydropyridine derivative which improve absorption by oral administration. Another object of the invention is to provide compositions wherein an unstable dihydropyridine derivative is stabilized therein.

25 The present inventors have conducted intensive studies to provide effective absorption of a slightly water-soluble drug from digestive tract and found that excellent bioavailability (BA) in oral use and stability of the drug can be achieved when the slightly water-soluble drug is formulated into a non-micelle composition by adding a fatty acid monoglyceride and/or a polyoxyethylenesorbitan fatty acid ester to the slightly water-soluble drug, or formulated into a composition by further adsorbing same onto a porous inorganic substance, and that the thus-obtained composition serves well as a pharmaceutical composition for oral use.

30 The present invention has been completed on the basis of such findings, and the present invention relates to a pharmaceutical composition for oral administration comprising:

- (1) a slightly water soluble drug being a dihydropyridine derivative set forth below;
- 35 (b) at least one surfactant selected from a fatty acid monoglyceride and a polyoxyethylenesorbitan fatty acid ester; and
- (c) a pharmaceutically acceptable porous inorganic substance.

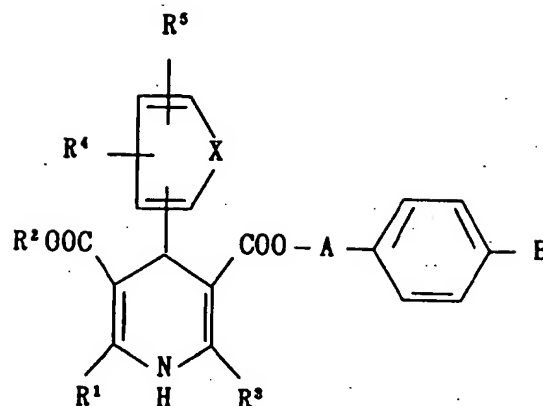
DETAILED DESCRIPTION OF THE INVENTION

40 The slightly water-soluble drug in the invention is a dihydropyridine derivative which has a solubility of 0.1 mg/ml or below in water and is pharmacologically active. Specifically, the dihydropyridine derivative is slightly absorbed by oral administration, has BA (%) of 10 or below, preferably 5 or below, more preferably 3 or below, when orally administered after pulverization with a mortar [into 200 mesh (75 μ m) or below] and suspending same in an aqueous solution of 0.5 % sodium carboxymethylcellulose, and is easily dissolved in a fatty acid monoglyceride and a polyoxyethylenesorbitan fatty acid ester.

45 The dihydropyridine derivate is a compound of the formula:

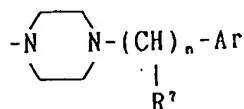
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55



wherein

R^1 , R^2 and R^3 are the same or different and are an alkyl, a cycloalkyl or an alkoxyalkyl;
 R^4 and R^5 are the same or different and are hydrogen, halogen, nitro, a halogenated alkyl, an alkylsulfonyl, a halogenated alkoxy, an alkylsulfinyl, an alkyl, a cycloalkyl, an alkoxy, cyano, an alkoxy carbonyl or an alkylthio, provided that R^4 and R^5 are not hydrogen at the same time;
 X is a group of vinylene or azomethine;
 A is an alkylene; and
 B is $-N(R^6)_2$ or



where

R^6 and R^7 are respectively hydrogen, an alkyl, a cycloalkyl, an aralkyl, an aryl or pyridyl, Ar is an aryl or pyridyl and n is an integer of 0 to 2;
 or their acid addition salts (USP 4886819, EP 257 616).

The alkyl represented by R^1 , R^2 or R^3 is preferably a lower alkyl having 1 to 6 carbon atoms, with further preference given to that having 1 to 4 carbon atoms. The lower alkyl may have a lower cycloalkyl having 3 to 6 carbon atoms on the alkyl terminal. As the cycloalkyl, a lower cycloalkyl having 3 to 6 carbon atoms is preferable. As the alkoxyalkyl, preferred are those having 3 to 7 carbon atoms.

The substituent represented by R^4 or R^5 is preferably at the 2- and/or 3-position to the binding site with the dihydropyridine ring. As the halogen at R^4 or R^5 , particularly preferred are fluorine or chlorine atom, and as the alkyl and cycloalkyl, preferred are those mentioned as R^1 to R^3 . The alkoxy and the alkylthio preferably possess a lower alkyl having 1 to 3 carbon atoms.

As the alkoxy carbonyl, there may be mentioned those having 2 to 4 carbon atoms. The halogen in halogenides is exemplified by those mentioned above, and the halogenated alkyl and the halogenated alkoxy may be that where some of the hydrogen atoms are halogenated or all of the hydrogen atoms are halogenated. The alkyl in alkylsulfonyl and alkylsulfinyl includes those exemplified as R^1 to R^3 .

As R^4 and R^5 , preferred are cyano and halogenated alkyl (specifically, trifluoromethyl).

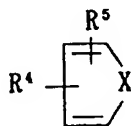
The alkyl and the cycloalkyl represented by R^6 and R^7 include those exemplified as R^1 to R^3 . Phenyl C_{1-3} alkyl is preferred as the aralkyl, and phenyl and naphthyl are preferred as aryl. These aromatic rings may have the same or different substituents at an optional position. The substituents on the aromatic ring include those mentioned as R^4 and R^5 . The pyridyl includes 2-pyridyl, 3-pyridyl and 4-pyridyl, which may have the substituents mentioned above as R^4 and R^5 .

The alkylene represented by A includes those having 2 to 4 carbon atoms, which may be a straight- or branched-

chain.

The aryl and the pyridyl represented by Ar include those exemplified as R⁶ and R⁷ and may have the same substituents.

The ring represented by



which is the 4-position substituent of dihydropyridine, means a benzene ring when X is vinylene (-CH=CH-) and pyridine when X is azomethine (-CH=N-). An optional position of the ring may bind to the 4-position of the dihydropyridine.

The substituents R⁴ and R⁵ are preferably at the ortho- and/or meta-position to a carbon atom binding to the 4-position of the dihydropyridine.

As such compounds, the following can be mentioned:

- o 2-(p-Dimethylaminophenyl)ethyl methyl 2,6-dimethyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride
- o 2-(p-Dimethylaminophenyl)ethyl methyl 2,6-dimethyl-4-(2-trifluoromethyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride
- o 2-(p-Dibenzylaminophenyl)ethyl methyl 2,6-dimethyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride
- o 2-(p-Dibenzylaminophenyl)ethyl methyl 2,6-dimethyl-4-(2-trifluoromethyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride
- o 2-[p-(4-Benzhydrylpiperazino)phenyl]ethyl methyl 2,6-dimethyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride
- o 2-[p-(4-Benzhydrylpiperazino)phenyl]ethyl methyl 2,6-dimethyl-4-(2-trifluoromethyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its fumarate
- o 2-[p-(4-Benzhydrylpiperazino)phenyl]ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride

The fatty acid monoglyceride is a monoester of fatty acid and glycerin where the fatty acid preferably has 14 to 28 carbon atoms, more preferably 16 to 18 carbon atoms and the number of unsaturated bonds, particularly double bonds, when the fatty acid is unsaturated is 1 or 2. Specific examples of unsaturated fatty acid include palmitoleic acid, oleic acid, linoleic acid and linolenic acid, and examples of saturated fatty acid include myristic acid, palmitic acid, stearic acid, behenic acid and heptacosanoic acid. As the fatty acid, those having the above carbon atoms may be used solely or in mixture, with preference given to unsaturated fatty acids.

In the present invention, the fatty acid moiety of the polyoxyethylenesorbitan fatty acid ester preferably has 10 to 18 carbon atoms, which is exemplified by polyoxyethylenesorbitan fatty acid esters such as polyoxyethylenesorbitan monooleate, polyoxyethylenesorbitan monostearate, polyoxyethylenesorbitan monopalmitate and polyoxyethylene-sorbitan monolaurate.

Further, a nonionic surfactant other than the above-mentioned polyoxyethylenesorbitan fatty acid esters may be co-used, and examples of such surfactants include polyoxyethylenesorbit fatty acid ester, polyoxyethylene hydrogenated castor oil and polyglycerin fatty acid ester.

The nonionic surfactant to be used in the present invention is not particularly limited and those acceptable as pharmaceutical additives may be used. The HLB value (hydrophile-lipophile balance) is preferably not less than 3, preferably 10 to 20.

The solubility of the slightly water-soluble drug in a fatty acid monoglyceride and a nonionic surfactant is 10-500 mg/ml.

No limitation is posed on the porous inorganic substance of the present invention as long as the substance efficiently adsorbs the non-micelle compositions obtained by adding a fatty acid monoglyceride and/or a polyoxyethylene-sorbitan fatty acid ester and is pharmacologically acceptable, and examples include magnesium aluminat silicate, silicon dioxides such as light silicic acid anhydride and silicon dioxide hydrate.

The proportion of each ingredient in the non-micelle compositions is not particularly limited but adjusted suitably depending on the kind of the slightly water-soluble drug.

For example, when either the fatty acid monoglyceride or the polyoxyethylenesorbitan fatty acid ester is used solely, it is preferably used in an amount of 1 to 100 parts by weight, preferably 5 to 60 parts by weight per 1 part by weight of

the slightly water-soluble drug. When the fatty acid monoglyceride and the polyoxyethylenesorbitan fatty acid ester are used combinedly, they are preferably used in an amount of 1 to 100 parts by weight, preferably 10 to 50 parts by weight per 1 part by weight of the slightly water-soluble drug.

Further, when a nonionic surfactant other than the polyoxyethylenesorbitan fatty acid ester is also used, a fatty acid monoglyceride and/or a polyoxyethylenesorbitan fatty acid ester and a nonionic surfactant are used in an amount of 1 to 100 parts by weight, preferably 10 to 50 parts by weight per 1 part by weight of the slightly water-soluble drug.

In the pharmaceutical composition for oral administration prepared by adsorption onto the porous inorganic substance, the porous inorganic substance is used in an amount of 1 to 100 parts by weight, preferably 2 to 10 parts by weight per 10 parts by weight of the aforementioned non-micelle composition comprising slightly water-soluble drug and surfactant.

The non-micelle compositions are normally prepared by dissolving a slightly water-soluble drug in a fatty acid monoglyceride and/or a polyoxyethylenesorbitan fatty acid ester, and a nonionic surfactant other than the polyoxyethylenesorbitan fatty acid ester. Other additives such as stabilizers, antiseptics and extenders, may be further added to the composition.

The pharmaceutical compositions of the invention prepared by adsorption onto a porous inorganic substance is normally in the form of powders and granules and the adsorption is conducted by a method known per se. That is, the pharmaceutical composition of the invention is prepared by mixing a non-micelle composition with a porous inorganic substance. The powders thus obtained may be formulated into powder preparations by adding an excipient for formulation such as mannitol, packed in capsules or tableted by a conventional method.

Example 1

2-[p-(4-Benzhydrylpiperazinophenyl)ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] hydrochloride (20.1 g) is added to unsaturated fatty acid monoglyceride (Kao, "Excel O-95R", 650 g), followed by dissolution and stirring at 40°C to give a non-micelle solution.

Example 2

2-[p-(4-Benzhydrylpiperazinophenyl)ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] hydrochloride (20.1 g) is added to polyoxyethylenesorbitan monooleate (Nikko Chemical, "TO-10M", 650 g), followed by dissolution and stirring at 40°C to give a non-micelle solution.

Example 3

2-[p-(4-Benzhydrylpiperazinophenyl)ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] hydrochloride (20.1 g) is added to a mixture of unsaturated fatty acid monoglyceride (Kao, "Excel O-95R") and polyoxyethylenesorbitan monooleate (Nikko Chemical, "TO-10M") in a proportion of 1:1 (650 g), followed by dissolution and stirring at 40°C to give a non-micelle solution.

Example 4

2-[p-(4-Benzhydrylpiperazinophenyl)ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] hydrochloride (20.1 g) is added to a mixture of unsaturated fatty acid monoglyceride (Kao, "Excel O-95R") and polyethylene glycol (PEG 400) in a proportion of 1:1 (650 g), followed by dissolution and stirring at 40°C to give a non-micelle solution.

Comparison Example 1

2-[p-(4-Benzhydrylpiperazinophenyl)ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] hydrochloride (20.1 g) is added to polyethylene glycol (PEG 400, 650 g), followed by dissolution and stirring at 40°C to give a non-micelle solution.

Comparison Example 2

2-[p-(4-Benzhydrylpiperazinophenyl)ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] hydrochloride (10 g) is pulverized with a mortar and mixed with lactose (190 g) to give 200 g of a powder for capsules.

Example 5

2-[p-(4-Benzhydrylpiperazinophenyl)ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] hydrochloride (20.1 g) is added to unsaturated fatty acid monoglyceride (Kao, "Excel O-95R", 650 g), followed by dissolution and stirring at 40°C to give a non-micelle solution. The thus-obtained solution (600 g) and magnesium alminate metasilicate (Fuji Kagaku Sangyo, "Neusilin US₂", 370 g) are mixed with a stirring-granulator. Thereto is added Carmellose sodium A type (30 g) for mixing and stirring, followed by addition of purified water (250 ml) to give granules. The granules are dried at 40°C for 17 hours with a forced-air drier and passed through a sieve of 355-75 µm (42-200 mesh) to give 550 g of fine granules for capsules.

Example 6

2-[p-(4-Benzhydrylpiperazinophenyl)ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] hydrochloride (20.1 g) is added to polyoxyethylenesorbitan monooleate (Nikko Chemical, "TO-10M", 650 g), followed by dissolution and stirring at 40°C to give a non-micelle solution. The thus-obtained solution (600 g) and magnesium alminate metasilicate (Fuji Kagaku Sangyo, "Neusilin US₂", 370 g) are mixed with a stirring-granulator. Thereto is added Carmellose sodium A type (30 g) for mixing and stirring, followed by addition of purified water (250 ml) to give granules. The granules are dried at 40°C for 17 hours with a forced-air drier and passed through a sieve 355-75 µm (42-200 mesh) to give 550 g of fine granules for capsules.

Example 7

2-[p-(4-Benzhydrylpiperazinophenyl)ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] hydrochloride (20.1 g) is added to a mixture of unsaturated fatty acid monoglyceride (Kao, "Excel O-95R") and polyoxyethylenesorbitan monooleate (Nikko Chemical, "TO-10M") in a proportion of 1:1 (650 g), followed by dissolution and stirring at 40°C to give a non-micelle solution. The thus-obtained solution (600 g) and magnesium alminate metasilicate (Fuji Kagaku Sangyo, "Neusilin US₂", 370 g) are mixed with a stirring-granulator. Thereto is added Carmellose sodium A type (30 g) for mixing and stirring, followed by addition of purified water (250 ml) to give granules. The granules are dried at 40°C for 17 hours with a forced-air drier and passed through a sieve of 355-75 µm (42-200 mesh) to give 550 g of fine granules for capsules.

Experiment Example 1

Absorption by oral administration

The absorption and stability of the pharmaceutical compositions as obtained in Examples 1 to 7 and Comparison Examples 1 and 2 are summarized in Table 1.

The absorption evaluation was conducted as follows. That is, a composition of the present invention was administered to a beagle weighing about 10 kg after fasted for 20 hours before the administration in a dose of 3 mg/0.1 ml/kg, and sample blood was taken from radial cutaneous vein at given time intervals up to 24 hours after the administration. The plasma of the blood sample was centrifuged, deproteinized with acetonitrile and determined by high performance liquid chromatography (HPLC) using a reversed-phase column [ODS (C₁₈), 4 µ, 3.9 Ø × 150 mm, Japan Waters]. The BA% was estimated on the basis of the blood concentration.

Table 1

	Additives used	Absorption (BA%)
Ex. 1	Excel O-95R	26.0
Ex. 2	TO-10M	24.3
Ex. 3	Excel O-95R+TO-10M (1:1)	25.6
Ex. 4	PEG 400+Excel O-95R (1:1)	21.7
Ex. 5	Excel O-95R/Neusilin	23.0
Ex. 7	Excel O-95R+TO-10M (1:1)/Neusilin	29.4
Comp. Ex. 1	PEG 400	1.2

Table 1 (continued)

	Additives used	Absorption (BA%)
Comp. Ex. 2	no additive	0.3

Experiment Example 2

Stability of the pharmaceutical composition of the invention

Using the pharmaceutical compositions as prepared in Examples 5 to 7, the stability was examined by a storage test at 40°C. The content of analogous substance and appearance 4 weeks later are summarized in Table 2.

Table 2

Additives used	Stability (60°C, 4 weeks)	
	content of analogous substance (%)*	appearance
Excel O-95R/Neusilin (Ex. 5)	2.9	colored
TO-10M/Neusilin (Ex. 6)	1.2	no change
Excel O-95R + TO-10M (1:1)/Neusilin (Ex. 7)	1.6	no change

* : dihydropyridine decomposing substance

The pharmaceutical compositions for oral administration of the present invention markedly improve absorption of slightly water-soluble drugs such as dihydropyridine etc. as evidenced in Experiment Example 1 and the stability of the slightly water-soluble drugs in a powdery form is excellent as evidenced in Experiment Example 2.

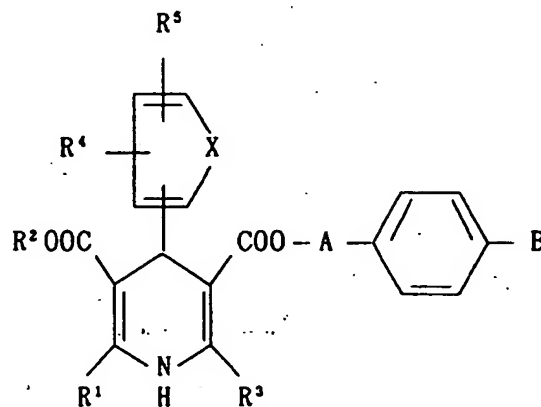
The use of the pharmaceutical compositions for oral administration of the present invention enables decreasing of the dose amount of slightly water-soluble drugs, which eventually leads to alleviation of pains and side effects on the part of patients.

Claims

Claims for the following Contracting States : BE, CH, DE, DK, FR, GB, IT, LI, NL, SE

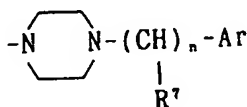
1. A pharmaceutical composition for oral administration comprising:

(a) a slightly water-soluble drug being a dihydropyridine derivative of the formula



wherein

R^1 , R^2 and R^3 are the same or different and are an alkyl, a cycloalkyl or an alkoxyalkyl;
 R^4 and R^5 are the same or different and are hydrogen, halogen, nitro, a halogenated alkyl, an alkylsulfonyl,
 a halogenated alkoxy, an alkylsulfinyl, an alkyl, a cycloalkyl, an alkoxy, cyano, an alkoxycarbonyl or an
 alkylthio, provided that R^4 and R^5 are not hydrogen at the same time;
 X is a group consisting of vinylene or azomethine;
 A is an alkylene; and
 B is $-N(R^6)_2$ or



where

R^6 and R^7 are respectively hydrogen, an alkyl, a cycloalkyl, an aralkyl, an aryl or pyridyl, Ar is an aryl or
 pyridyl and n is an integer of 0 to 2;
 or their acid addition salts,

- (b) at least one surfactant selected from fatty acid monoglyceride and polyoxyethylenesorbitan fatty acid ester,
 and
 (c) a porous inorganic substance.

2. A pharmaceutical composition for oral administration as claimed in Claim 1, wherein the slightly water-soluble drug has bioavailability (%) of 10 or below, when orally administered after pulverization into 200 mesh (75 μ m) or below and suspending same in an aqueous solution of 0.5% sodium carboxymethylcellulose.
3. A pharmaceutical composition for oral administration as claimed in Claim 1, which is obtained by (a) dissolving the slightly water-soluble drug in a surfactant to prepare a non-micelle composition and (b) adsorbing the non-micelle composition of step (a) onto the porous inorganic substance.
4. A pharmaceutical composition for oral administration as claimed in Claim 1, wherein the slightly water-soluble drug is selected from

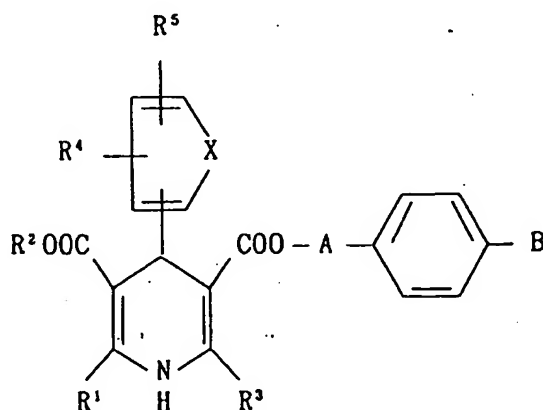
2-(p-Dimethylaminophenyl)ethyl methyl 2,6-dimethyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride,
 2-(p-Dimethylaminophenyl)ethyl methyl 2,6-dimethyl-4-(2-trifluoromethyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride,
 2-(p-Dibenzylaminophenyl)ethyl methyl 2,6-dimethyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride,
 2-(p-Dibenzylaminophenyl)ethyl methyl 2,6-dimethyl-4-(2-trifluoromethyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride,
 2-[p-(4-Benzhydrylpiperazino)phenyl]ethyl methyl 2,6-dimethyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride,
 2-[p-(4-Benzhydrylpiperazino)phenyl]ethyl methyl 2,6-dimethyl-4-(2-trifluoromethyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its fumarate, and
 2-[p-(4-Benzhydrylpiperazino)phenyl]ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride.

5. A pharmaceutical composition for oral administration as claimed in Claim 1, wherein the fatty acid monoglyceride is of a fatty acid having 14 to 28 carbon atoms.
6. A pharmaceutical composition for oral administration as claimed in Claim 5, wherein the fatty acid having 14 to 28 carbon atoms is selected from palmitoleic acid, oleic acid, linoleic acid and linolenic acid.
7. A pharmaceutical composition for oral administration as claimed in Claim 1, wherein the polyoxyethylenesorbitan fatty acid ester is of a fatty acid having 10 to 18 carbon atoms.

8. A pharmaceutical composition for oral administration as claimed in Claim 7, wherein the fatty acid having 10 to 18 carbon atoms is selected from polyoxyethylenesorbitan fatty acid esters such as polyoxyethylenesorbitan monooleate, polyoxyethylenesorbitan monostearate, polyoxyethylenesorbitan monopalmitate and polyoxyethylenesorbitan monolaurate.
9. A pharmaceutical composition for oral administration as claimed in Claim 1, wherein a nonionic surfactant other than the polyoxyethylenesorbitan fatty acid ester is added.
10. A pharmaceutical composition for oral administration as claimed in Claim 9, wherein the nonionic surfactant has HLB (hydrophile-lipophile balance) of not less than 3.
11. A pharmaceutical composition for oral administration as claimed in Claim 9, wherein the nonionic surfactant is selected from polyoxyethylenesorbit fatty acid ester, polyoxyethylene hydrogenated castor oil and polyglycerin fatty acid ester.
12. A pharmaceutical composition for oral administration as claimed in Claim 1, wherein the fatty acid monoglyceride and/or the polyoxyethylenesorbitan fatty acid ester is used in an amount of 1 to 100 parts by weight per 1 part by weight of the slightly water-soluble drug.
13. A pharmaceutical composition for oral administration as claimed in Claim 9, wherein the fatty acid monoglyceride and the nonionic surfactant other than polyoxyethylenesorbitan fatty acid ester are used in an amount of 1 to 100 parts by weight per 1 part by weight of the slightly water-soluble drug.
14. A pharmaceutical composition for oral administration as claimed in Claim 1, wherein the surfactant is a combination of fatty acid monoglyceride and polyoxyethylenesorbitan fatty acid ester.
15. A pharmaceutical composition for oral administration as claimed in Claim 3, wherein the porous inorganic substance is mixed in an amount of 1 to 100 parts by weight per 10 parts by weight of the non-micelle composition.
16. A pharmaceutical composition for oral administration as claimed in Claim 1, wherein the porous inorganic substance is selected from magnesium aluminate silicate and silicon dioxide.

Claims for the following Contracting State : ES

1. A process for preparing a pharmaceutical composition for oral administration comprising:
- (a) a slightly water-soluble drug being a dihydropyridine derivative of the formula



wherein

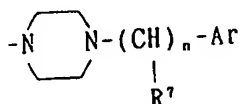
R¹, R² and R³ are the same or different and are an alkyl, a cycloalkyl or an alkoxyalkyl;

R^4 and R^5 are the same or different and are hydrogen, halogen, nitro, a halogenated alkyl, an alkylsulfonyl, a halogenated alkoxy, an alkylsulfinyl, an alkyl, a cycloalkyl, an alkoxy, cyano, an alkoxycarbonyl or an alkylthio, provided that R^4 and R^5 are not hydrogen at the same time;

X is a group consisting of vinylene or azomethine;

A is an alkylene; and

B is $-N(R^6)_2$ or



where

R^6 and R^7 are respectively hydrogen, an alkyl, a cycloalkyl, an aralkyl, an aryl or pyridyl, Ar is an aryl or pyridyl and n is an integer of 0 to 2;
or their acid addition salts,

(b) at least one surfactant selected from fatty acid monoglyceride and polyoxyethylenesorbitan fatty acid ester, and

(c) a porous inorganic substance, which process comprises

- (i) dissolving the slightly water-soluble drug in a surfactant to prepare a non-micelle composition and
- (ii) adsorbing the non-micelle composition of step (i) onto the porous inorganic substance.

2. A process as claimed in claim 1, wherein the slightly water-soluble drug has bioavailability (%) of 10 or below, when orally administered after pulverization into 200 mesh (75 μm) or below and suspending same in an aqueous solution of 0.5% sodium carboxymethylcellulose.

3. A process as claimed in claim 1, wherein the slightly water-soluble drug is selected from:

2-(p-Dimethylaminophenyl)ethyl methyl 2,6-dimethyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride,

2-(p-Dimethylaminophenyl)ethyl methyl 2,6-dimethyl-4-(2-trifluoromethyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride,

2-(p-Dibenzylaminophenyl)ethyl methyl 2,6-dimethyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride,

2-(p-Dibenzylaminophenyl)ethyl methyl 2,6-dimethyl-4-(2-trifluoromethyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride,

2-[p-(4-Benzhydrylpiperazino)phenyl]ethyl methyl 2,6-dimethyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride,

2-[p-(4-Benzhydrylpiperazino)phenyl]ethyl methyl 2,6-dimethyl-4-(2-trifluoromethyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate and its fumarate, and

2-[p-(4-Benzhydrylpiperazino)phenyl]ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and its hydrochloride.

4. A process as claimed in Claim 1, wherein the fatty acid monoglyceride is of a fatty acid having 14 to 28 carbon atoms.

5. A process as claimed in Claim 4, wherein the fatty acid having 14 to 28 carbon atoms is selected from palmitoleic acid, oleic acid, linoleic acid and linolenic acid.

6. A process as claimed in Claim 1, wherein the polyoxyethylenesorbitan fatty acid ester is of a fatty acid having 10 to 18 carbon atoms.

7. A process as claimed in Claim 6, wherein the fatty acid having 10 to 18 carbon atoms is selected from polyoxyethylenesorbitan fatty acid esters such as polyoxyethylenesorbitan monooleate, polyoxyethylenesorbitan monostearate, polyoxyethylenesorbitan monopalmitate and polyoxyethylenesorbitan monolaurate.

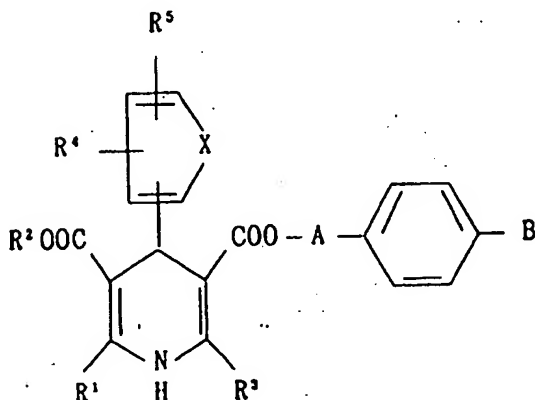
8. A process as claimed in Claim 1, wherein a nonionic surfactant other than the polyoxyethylenesorbitan fatty acid ester is added.
9. A process as claimed in Claim 8, wherein the nonionic surfactant has HLB (hydrophile-lipophile balance) of not less than 3.
10. A process as claimed in Claim 8, wherein the nonionic surfactant is selected from polyoxyethylenesorbit fatty acid ester, polyoxyethylene hydrogenated castor oil and polyglycerin fatty acid ester.
11. A process as claimed in Claim 1, wherein the fatty acid monoglyceride and/or the polyoxyethylenesorbitan fatty acid ester is used in an amount of 1 to 100 parts by weight per 1 part by weight of the slightly water-soluble drug.
12. A process as claimed in Claim 8, wherein the fatty acid monoglyceride and the nonionic surfactant other than polyoxyethylenesorbitan fatty acid ester are used in an amount of 1 to 100 parts by weight per 1 part by weight of the slightly water-soluble drug.
13. A process as claimed in Claim 1, wherein the surfactant is a combination of fatty acid monoglyceride and polyoxyethylenesorbitan fatty acid ester.
14. A process as claimed in Claim 1, wherein the porous inorganic substance is mixed in an amount of 1 to 100 parts by weight per 10 parts by weight of the non-micelle composition.
15. A process as claimed in Claim 1, wherein the porous inorganic substance is selected from magnesium aluminate silicate and silicon dioxide.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, DK, FR, GB, IT, LI, NL, SE

1. Pharmazeutische Zusammensetzung für orale Verabreichung, umfassend:

(a) ein in Wasser schwerlösliches Medikament, bei dem es sich um ein Dihydropyridin-Derivat der Formel



handelt, wobei

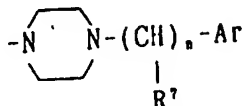
R¹, R² und R³ gleich oder verschieden sind und ein Alkyl, Cycloalkyl oder Alkoxyalkyl darstellen,

R⁴ und R⁵ gleich oder verschieden sind und Wasserstoff, Halogen, Nitro, halogeniertes Alkyl, Alkylsulfonyl, halogeniertes Alkoxy, Alkylsulfinyl, Alkyl, Cycloalkyl, Alkoxy, Cyan, Alkoxy-carbonyl oder Alkylthio darstellen, mit der Maßgabe, daß R⁴ und R⁵ nicht gleichzeitig Wasserstoff sind,

X eine Vinylen- oder Azomethingruppe ist,

A ein Alkylen ist und

B -N(R⁶)₂ oder



ist, wobei

R⁶ und R⁷ jeweils Wasserstoff, Alkyl, Cycloalkyl, Aralkyl, Aryl oder Pyridyl sind, Ar Aryl oder Pyridyl ist und n eine ganze Zahl von 0 bis 2 ist; oder deren Säureadditionssalze;

(b) wenigstens ein Tensid, das aus Fettsäuremonoglycerid und Polyoxyethylensorbitanfettsäureester ausgewählt ist; sowie

(c) eine poröse anorganische Substanz.

2. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 1, wobei das in Wasser schwerlösliche Medikament eine Bioverfügbarkeit (%) von 10 oder weniger besitzt, wenn es nach der Pulverisierung zu 200 mesh (75 µm) oder kleiner und Suspendieren des Pulvers in einer wäßrigen Lösung von 0,5% Natriumcarboxymethylcellulose oral verabreicht wird.

3. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 1, die man erhält durch (a) Auflösen des in Wasser schwerlöslichen Medikaments in einem Tensid unter Bildung einer Nicht-Micellen-Zusammensetzung und (b) Adsorbieren der Nicht-Micellen-Zusammensetzung von Schritt (a) an der porösen anorganischen Substanz.

4. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 1, wobei das in Wasser schwerlösliche Medikament ausgewählt ist aus

2-(p-Dimethylaminophenyl)ethylmethyl-2,6-dimethyl-4-(4-cyan-2-pyridyl)-1,4-dihydropyridin-3,5-dicarboxylat und seinem Hydrochlorid,

2-(p-Dimethylaminophenyl)ethylmethyl-2,6-dimethyl-4-(2-trifluormethyl-3-pyridyl)-1,4-dihydropyridin-3,5-dicarboxylat und seinem Hydrochlorid,

2-(p-Dibenzylaminophenyl)ethylmethyl-2,6-dimethyl-4-(4-cyan-2-pyridyl)-1,4-dihydropyridin-3,5-dicarboxylat und seinem Hydrochlorid,

2-(p-Dibenzylaminophenyl)ethylmethyl-2,6-dimethyl-4-(2-trifluormethyl-3-pyridyl)-1,4-dihydropyridin-3,5-dicarboxylat und seinem Hydrochlorid,

2-[p-(4-Benzhydrylpiperazino)phenyl]ethylmethyl-2,6-dimethyl-4-(4-cyan-2-pyridyl)-1,4-dihydropyridin-3,5-dicarboxylat und seinem Hydrochlorid,

2-[p-(4-Benzhydrylpiperazino)phenyl]ethylmethyl-2,6-dimethyl-4-(2-trifluormethyl-3-pyridyl)-1,4-dihydropyridin-3,5-dicarboxylat und seinem Fumarat sowie

2-[p-(4-Benzhydrylpiperazino)phenyl]ethylmethyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridin-3,5-dicarboxylat und seinem Hydrochlorid.

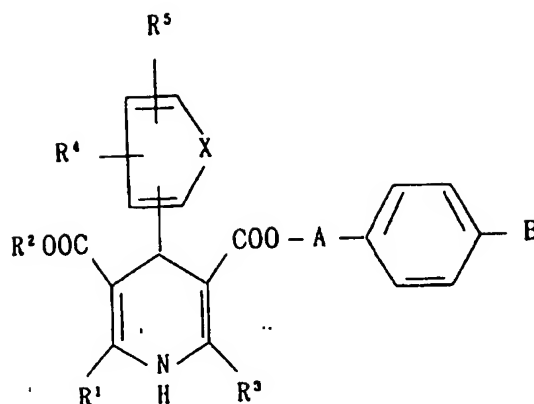
5. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 1, wobei das Fettsäuremonoglycerid von einer Fettsäure mit 14 bis 28 Kohlenstoffatomen abgeleitet ist.

6. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 5, wobei die Fettsäure mit 14 bis 28 Kohlenstoffatomen aus Palmitoleinsäure, Oleinsäure, Linolsäure und Linolensäure ausgewählt ist.

7. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 1, wobei der Polyoxyethylensorbitanfettsäureester von einer Fettsäure mit 10 bis 18 Kohlenstoffatomen abgeleitet ist.
8. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 7, wobei die Fettsäure mit 10 bis 18 Kohlenstoffatomen aus Polyoxyethylensorbitanfettsäureestern wie Polyoxyethylensorbitanmonooleat, Polyoxyethylensorbitanmonostearat, Polyoxyethylensorbitanmonopalmitat und Polyoxyethylensorbitanmonolaurat ausgewählt ist.
9. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 1, wobei ein anderes nichtionisches Tensid als der Polyoxyethylensorbitanfettsäureester hinzugefügt wird.
10. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 9, wobei das nichtionische Tensid einen HLB-Wert (Hydrophil-Lipophil-Gleichgewicht) von nicht weniger als 3 besitzt.
11. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 9, wobei das nichtionische Tensid aus Polyoxyethylensorbitfettsäureester, Polyoxyethylen-hydriertem-Ricinusöl und Polyglycerinfettsäureester ausgewählt ist.
12. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 1, wobei das Fettsäuremonoglycerid und/oder der Polyoxyethylensorbitanfettsäureester in einer Menge von 1 bis 100 Gewichtsteilen pro 1 Gewichtsteil des in Wasser schwerlöslichen Medikaments verwendet wird.
13. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 9, wobei das Fettsäuremonoglycerid und das andere nichtionische Tensid als Polyoxyethylensorbitanfettsäureester in einer Menge von 1 bis 100 Gewichtsteilen pro 1 Gewichtsteil des in Wasser schwerlöslichen Medikaments verwendet werden.
14. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 1, wobei das Tensid eine Kombination von Fettsäuremonoglycerid und Polyoxyethylensorbitanfettsäureester ist.
15. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 3, wobei die poröse anorganische Substanz in einer Menge von 1 bis 100 Gewichtsteilen pro 10 Gewichtsteile der Nicht-Micellen-Zusammensetzung zugemischt wird.
16. Pharmazeutische Zusammensetzung für orale Verabreichung gemäß Anspruch 1, wobei die poröse anorganische Substanz aus Magnesiumaluminatsilicat und Siliciumdioxid ausgewählt ist.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung für orale Verabreichung, umfassend:
- (a) ein in Wasser schwerlösliches Medikament, bei dem es sich um ein Dihydropyridin-Derivat der Formel



handelt, wobei

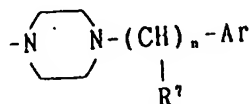
R^1 , R^2 und R^3 gleich oder verschieden sind und ein Alkyl, Cycloalkyl oder Alkoxyalkyl darstellen,

R^4 und R^5 gleich oder verschieden sind und Wasserstoff, Halogen, Nitro, halogeniertes Alkyl, Alkylsulfonyl, halogeniertes Alkoxy, Alkylsulfinyl, Alkyl, Cycloalkyl, Alkoxy, Cyan, Alkoxy-carbonyl oder Alkylthio darstellen, mit der Maßgabe, daß R^4 und R^5 nicht gleichzeitig Wasserstoff sind,

X eine Vinylen- oder Azomethingruppe ist,

A ein Alkylen ist und

B -N(R^6)₂ oder



ist, wobei

R^6 und R^7 jeweils Wasserstoff, Alkyl, Cycloalkyl, Aralkyl, Aryl oder Pyridyl sind, Ar Aryl oder Pyridyl ist und n eine ganze Zahl von 0 bis 2 ist; oder deren Säureadditionssalze;

(b) wenigstens ein Tensid, das aus Fettsäuremonoglycerid und Polyoxyethylensorbitanfettsäureester ausgewählt ist; sowie

(c) eine poröse anorganische Substanz, wobei das Verfahren (i) das Auflösen des in Wasser schwerlöslichen Medikaments in einem Tensid unter Bildung einer Nicht-Micellen-Zusammensetzung und (ii) das Adsorbieren der Nicht-Micellen-Zusammensetzung von Schritt (i) an der porösen anorganischen Substanz umfaßt.

2. Verfahren gemäß Anspruch 1, wobei das in Wasser schwerlösliche Medikament eine Bioverfügbarkeit (%) von 10 oder weniger besitzt, wenn es nach der Pulverisierung zu 200 mesh (75 μ m) oder kleiner und Suspendieren des Pulvers in einer wäßrigen Lösung von 0,5% Natriumcarboxymethylcellulose oral verabreicht wird.

3. Verfahren gemäß Anspruch 1, wobei das in Wasser schwerlösliche Medikament ausgewählt ist aus

2-(p-Dimethylaminophenyl)ethylmethyl-2,6-dimethyl-4-(4-cyan-2-pyridyl)-1,4-dihydropyridin-3,5-dicarboxylat

und seinem Hydrochlorid,

2-(p-Dimethylaminophenyl)ethylmethyl-2,6-dimethyl-4-(2-trifluormethyl-3-pyridyl)-1,4-dihydropyridin-3,5-dicarboxylat und seinem Hydrochlorid,

2-(p-Dibenzylaminophenyl)ethylmethyl-2,6-dimethyl-4-(4-cyan-2-pyridyl)-1,4-dihydropyridin-3,5-dicarboxylat und seinem Hydrochlorid,

2-(p-Dibenzylaminophenyl)ethylmethyl-2,6-dimethyl-4-(2-trifluormethyl-3-pyridyl)-1,4-dihydropyridin-3,5-dicarboxylat und seinem Hydrochlorid,

2-[p-(4-Benzhydrylpiperazino)phenyl]ethylmethyl-2,6-dimethyl-4-(4-cyan-2-pyridyl)-1,4-dihydropyridin-3,5-dicarboxylat und seinem Hydrochlorid,

2-[p-(4-Benzhydrylpiperazino)phenyl]ethylmethyl-2,6-dimethyl-4-(2-trifluormethyl-3-pyridyl)-1,4-dihydropyridin-3,5-dicarboxylat und seinem Fumarat sowie

2-[p-(4-Benzhydrylpiperazino)phenyl]ethylmethyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridin-3,5-dicarboxylat und seinem Hydrochlorid.

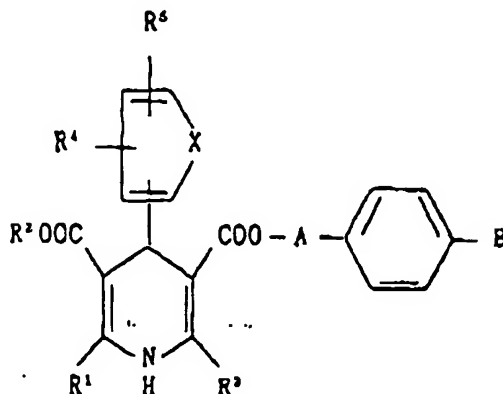
4. Verfahren gemäß Anspruch 1, wobei das Fettsäuremonoglycerid von einer Fettsäure mit 14 bis 28 Kohlenstoffatomen abgeleitet ist.
5. Verfahren gemäß Anspruch 4, wobei die Fettsäure mit 14 bis 28 Kohlenstoffatomen aus Palmitoleinsäure, Oleinsäure, Linolsäure und Linolensäure ausgewählt ist.
6. Verfahren gemäß Anspruch 1, wobei der Polyoxyethylensorbitanfettsäureester von einer Fettsäure mit 10 bis 18 Kohlenstoffatomen abgeleitet ist.
7. Verfahren gemäß Anspruch 6, wobei die Fettsäure mit 10 bis 18 Kohlenstoffatomen aus Polyoxyethylensorbitanfettsäureestern wie Polyoxyethylensorbitanmonooleat, Polyoxyethylensorbitanmonostearat, Polyoxyethylensorbitanmonopalmitat und Polyoxyethylensorbitanmonolaurat ausgewählt ist.
8. Verfahren gemäß Anspruch 1, wobei ein anderes nichtionisches Tensid als der Polyoxyethylensorbitanfettsäureester hinzugefügt wird.
9. Verfahren gemäß Anspruch 8, wobei das nichtionische Tensid einen HLB-Wert (Hydrophil-Lipophil-Gleichgewicht) von nicht weniger als 3 besitzt.
10. Verfahren gemäß Anspruch 8, wobei das nichtionische Tensid aus Polyoxyethylensorbitfettsäureester, Polyoxyethylen-hydriertem-Ricinusöl und Polyglycerinfettsäureester ausgewählt ist.
11. Verfahren gemäß Anspruch 1, wobei das Fettsäuremonoglycerid und/oder der Polyoxyethylensorbitanfettsäureester in einer Menge von 1 bis 100 Gewichtsteilen pro 1 Gewichtsteil des in Wasser schwerlöslichen Medikaments verwendet wird.
12. Verfahren gemäß Anspruch 8, wobei das Fettsäuremonoglycerid und das andere nichtionische Tensid als Polyoxyethylensorbitanfettsäureester in einer Menge von 1 bis 100 Gewichtsteilen pro 1 Gewichtsteil des in Wasser schwerlöslichen Medikaments verwendet werden.
13. Verfahren gemäß Anspruch 1, wobei das Tensid eine Kombination von Fettsäuremonoglycerid und Polyoxyethylensorbitanfettsäureester ist.
14. Verfahren gemäß Anspruch 1, wobei die poröse anorganische Substanz in einer Menge von 1 bis 100 Gewichtsteilen pro 10 Gewichtsteile der Nicht-Micellen-Zusammensetzung zugemischt wird.
15. Verfahren gemäß Anspruch 1, wobei die poröse anorganische Substanz aus Magnesiumaluminatsilicat und Siliciumdioxid ausgewählt ist.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, DK, FR, GB, IT, LI, NL, SE

1. Composition pharmaceutique pour l'administration orale comprenant :

(a) un médicament légèrement soluble dans l'eau qui est un dérivé de dihydropyridine de formule



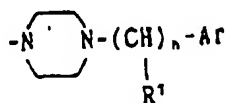
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R^1 , R^2 et R^3 sont identiques ou différents et représentent un alkyle, un cycloalkyle ou un alcoxyalkyle ;
 R^4 et R^5 sont identiques ou différents et représentent un hydrogène, un halogène, un nitro, un alkyle halogéné, un alkylsulfonyl, un alkoxy halogéné, un alkylsulfinyle, un alkyle, un cyclo-alkyle, un alkoxy, un cyano, un alcoxycarbonyl ou un alkylthio, à condition que R^4 et R^5 ne représentent pas un hydrogène en même temps ;

X est un groupe constitué de vinylène ou d'azométhine ;

A est un alkylène ; et

B représente $-N(R^6)_2$ ou



où

R^6 et R^7 représentent effectivement un hydrogène, un alkyle, un cycloalkyle, un aralkyle, un aryle ou un pyridyle, Ar est un aryle ou un pyridyle et n est un nombre entier compris entre 0 et 2 ;

ou ses sels d'addition d'acide,

(b) au moins un agent tensio-actif choisi parmi les monoglycérides d'acide gras et les esters d'acide gras de polyoxyéthylène sorbitane, et

(c) une substance inorganique poreuse.

2. Composition pharmaceutique pour l'administration orale selon la revendication 1, dans laquelle le médicament légèrement soluble dans l'eau possède une biodisponibilité (%) égale ou inférieure à 10, lorsqu'il est administré par voie orale après pulvérisation en une taille de $75 \mu\text{m}$ (200 mesh) ou en-dessous et il est mis en suspension dans une solution aqueuse de carboxyméthylcellulose sodique à 0,5%.

3. Composition pharmaceutique pour administration orale selon la revendication 1, que l'on obtient en (a) dissolvant le médicament légèrement soluble dans l'eau dans un agent tensio-actif pour préparer la composition non-micelle et (b) adsorbant la composition non-micelle de l'étape (a) sur la substance inorganique poreuse.

4. Composition pharmaceutique pour administration orale selon la revendication 1, dans laquelle le médicament légèrement soluble dans l'eau est choisi parmi

le 2-(p-diméthylaminophényl)éthyl méthyl 2,6-diméthyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicar-

boxylate et son chlorhydrate,

le 2-(p-diméthylaminophényl)éthyl méthyl 2,6-diméthyl-4-(2-trifluorométhyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate et son chlorhydrate,

le 2-(p-dibenzylaminophényl)éthyl méthyl 2,6-diméthyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate et son chlorhydrate,

le 2-(p-dibenzylaminophényl)éthyl méthyl 2,6-diméthyl-4-(2-trifluorométhyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate et son chlorhydrate,

le 2-[p-(4-benzhydrylpipérazino)phényl]éthyl méthyl 2,6-diméthyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate et son chlorhydrate,

le 2-[p-(4-benzhydrylpipérazino)phényl]éthyl méthyl 2,6-diméthyl-4-(2-trifluorométhyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate et son fumarate, et

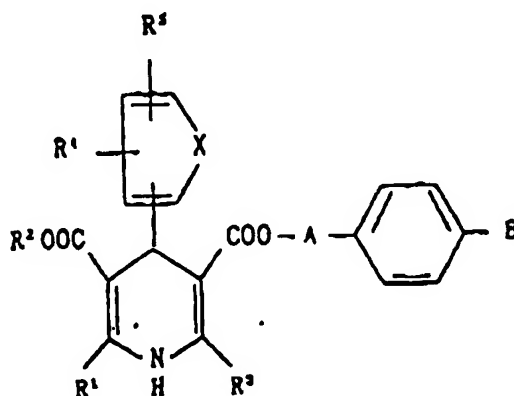
le 2-[p-(4-benzhydrylpipérazino)phényl]éthyl méthyl 2,6-diméthyl-4-(3-nitrophényl)-1,4-dihydropyridine-3,5-dicarboxylate et son chlorhydrate.

- 5 15 5. Composition pharmaceutique pour administration orale selon la revendication 1, dans laquelle le monoglycéride d'acide gras est un monoglycéride d'un acide gras ayant de 14 à 28 atomes de carbone.
6. Composition pharmaceutique pour administration orale selon la revendication 5, dans laquelle l'acide gras ayant de 14 à 28 atomes de carbone est choisi parmi l'acide palmitoléique, l'acide oléique, l'acide linoléique et l'acide linolénique.
7. Composition pharmaceutique pour administration orale selon la revendication 1, dans laquelle l'ester d'acide gras de polyoxyéthylène sorbitane est un ester d'un acide gras ayant de 10 à 18 atomes de carbone.
8. Composition pharmaceutique pour administration orale selon la revendication 7, dans laquelle l'acide gras ayant de 10 à 18 atomes de carbone est choisi parmi les esters d'acides gras de polyoxyéthylène sorbitane comme le monooléate de polyoxyéthylène sorbitane, le monostéarate de polyoxyéthylène sorbitane, le monopalmitate de polyoxyéthylène sorbitane et le monolaurate de polyoxyéthylène sorbitane.
9. Composition pharmaceutique pour administration orale selon la revendication 1, dans laquelle on ajoute un agent tensio-actif non ionique autre que l'ester d'acide gras de polyoxyéthylène sorbitane.
10. Composition pharmaceutique pour administration orale selon la revendication 9, dans laquelle l'agent tensio-actif non ionique possède un équilibre hydrophile-lipophile (EHL) au moins égal à trois.
11. Composition pharmaceutique pour administration orale selon la revendication 9, dans laquelle l'agent tensio-actif non ionique est choisi parmi un ester d'acide gras de polyoxyéthylène sorbitol, une huile de ricin hydrogénée avec du polyoxyéthylène et un ester d'acide gras de polyglycérine.
12. Composition pharmaceutique pour administration orale selon la revendication 1, dans laquelle le monoglycéride d'acide gras et/ou l'ester d'acide gras de polyoxyéthylène sorbitane est utilisé en une quantité de 1 à 100 parties en poids pour une partie en poids du médicament légèrement soluble dans l'eau.
13. Composition pharmaceutique pour administration orale selon la revendication 9, dans laquelle le monoglycéride d'acide gras et l'agent tensio-actif non ionique autre que l'ester d'acide gras de polyoxyéthylène sorbitane sont utilisés en une quantité de 1 à 100 parties en poids pour une partie en poids du médicament légèrement soluble dans l'eau.
14. Composition pharmaceutique pour administration orale selon la revendication 1, dans laquelle l'agent tensio-actif est une combinaison de monoglycéride d'acide gras et d'ester d'acide gras de polyoxyéthylène sorbitane.
15. Composition pharmaceutique pour administration orale selon la revendication 3, dans laquelle la substance inorganique poreuse est mélangée en une quantité de 1 à 100 parties en poids pour 10 parties en poids de la composition non-micelle.
16. Composition pharmaceutique pour administration orale selon la revendication 1, dans laquelle la substance inorganique poreuse est choisie parmi l'aluminate-silicate de magnésium et le dioxyde de silicium.

Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'une composition pharmaceutique pour l'administration orale comprenant :

(a) un médicament légèrement soluble dans l'eau qui est un dérivé de dihydropyridine de formule



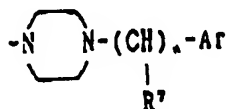
dans laquelle

R^1 , R^2 et R^3 sont identiques ou différents et représentent un alkyle, un cycloalkyle ou un alcoxyalkyle ;
 R^4 et R^5 sont identiques ou différents et représentent un hydrogène, un halogène, un nitro, un alkyle halogéné, un alkylsulfonyl, un alcoxy halogéné, un alkylsulfinyl, un alkyle, un cyclo-alkyle, un alcoxy, un cyano, un alcoxycarbonyl ou un alkylthio, à condition que R^4 et R^5 ne représentent pas un hydrogène en même temps ;

X est un groupe constitué de vinylène ou d'azométhine ;

A est un alkylène ; et

B représente $-N(R^6)_2$ ou



où

R^6 et R^7 représentent effectivement un hydrogène, un alkyle, un cycloalkyle, un aralkyle, un aryle ou un pyridyle, Ar est un aryle ou un pyridyle et n est un nombre entier compris entre 0 et 2 ;
 ou ses sels d'addition d'acide,

(b) au moins un agent tensio-actif choisi parmi les monoglycérides d'acides gras et les esters d'acides gras de polyoxyéthylène sorbitane, et

(c) une substance inorganique poreuse, dans lequel

(i) on dissout le médicament légèrement soluble dans l'eau dans un agent tensio-actif pour préparer une composition non-micelle, et

(ii) on adsorbe la composition non-micelle de l'étape (i) sur la substance inorganique poreuse.

2. Procédé selon la revendication 1, dans lequel le médicament légèrement soluble dans l'eau possède une biodisponibilité (%) égale ou inférieure à 10, lorsqu'il est administré par voie orale après pulvérisation en une taille de 75 μ m (200 mesh) ou en-dessous et qu'il est mis en suspension dans une solution aqueuse de carboxyméthylcellulose sodique à 0,5%.

3. Procédé selon la revendication 1, dans lequel le médicament légèrement soluble dans l'eau est choisi parmi

- le 2-(p-diméthylaminophényl)éthyl méthyl 2,6-diméthyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate et son chlorhydrate,
- le 2-(p-diméthylaminophényl)éthyl méthyl 2,6-diméthyl-4-(2-trifluorométhyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate et son chlorhydrate,
- le 2-(p-dibenzylaminophényl)éthyl méthyl 2,6-diméthyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate et son chlorhydrate,
- le 2-(p-dibenzylaminophényl)éthyl méthyl 2,6-diméthyl-4-(2-trifluorométhyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate et son chlorhydrate,
- le 2-[p-(4-benzhydrylpipérazino)phényl]éthyl méthyl 2,6-diméthyl-4-(4-cyano-2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate et son chlorhydrate,
- le 2-[p-(4-benzhydrylpipérazino)phényl]éthyl méthyl 2,6-diméthyl-4-(2-trifluorométhyl-3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate et son fumarate, et
- le 2-[p-(4-benzhydrylpipérazino)phényl]éthyl méthyl 2,6-diméthyl-4-(3-nitrophényl)-1,4-dihydropyridine-3,5-dicarboxylate et son chlorhydrate.

4. Procédé selon la revendication 1, dans lequel le monoglycéride d'acide gras est un monoglycéride d'un acide gras ayant de 14 à 28 atomes de carbone.

5. Procédé selon la revendication 4, dans lequel l'acide gras ayant de 14 à 28 atomes de carbone est choisi parmi l'acide palmitoléique, l'acide oléique, l'acide linoléique et l'acide linolénique.

6. Procédé selon la revendication 1, dans lequel l'ester d'acide gras de polyoxyéthylène sorbitane est un ester d'un acide gras ayant de 10 à 18 atomes de carbone.

7. Procédé selon la revendication 6, dans lequel l'acide gras ayant de 10 à 18 atomes de carbone est choisi parmi les esters d'acides gras de polyoxyéthylène sorbitane comme le monooléate de polyoxyéthylène sorbitane, le monostéarate de polyoxyéthylène sorbitane, le monopalmitate de polyoxyéthylène sorbitane et le monolaurate de polyoxyéthylène sorbitane.

8. Procédé selon la revendication 1, dans lequel on ajoute un agent tensio-actif non ionique autre que l'ester d'acide gras de polyoxyéthylène sorbitane.

9. Procédé selon la revendication 8, dans lequel l'agent tensio-actif non ionique possède un équilibre hydrophile-lipophile (EHL) au moins égal à trois.

10. Procédé selon la revendication 8, dans lequel l'agent tensio-actif non ionique est choisi parmi les esters d'acides gras de polyoxyéthylène sorbitol, l'huile de ricin hydrogénée avec du polyoxyéthylène et un ester d'acide gras de polyglycérine.

11. Procédé selon la revendication 1, dans lequel on utilise le monoglycéride d'acide gras et/ou l'ester d'acide gras de polyoxyéthylène sorbitane en une quantité de 1 à 100 parties en poids pour une partie en poids du médicament légèrement soluble dans l'eau.

12. Procédé selon la revendication 8, dans lequel on utilise le monoglycéride d'acide gras et l'agent tensio-actif non ionique autre que l'ester d'acide gras de polyoxyéthylène sorbitane en une quantité de 1 à 100 parties en poids pour une partie en poids du médicament légèrement soluble dans l'eau.

13. Procédé selon la revendication 1, dans lequel l'agent tensio-actif est une combinaison de monoglycérides d'acide gras et d'esters d'acide gras de polyoxyéthylène sorbitane.

14. Procédé selon la revendication 1, dans lequel on mélange la substance inorganique poreuse en une quantité de 1 à 100 parties en poids pour 10 parties en poids de la composition non-micelle.

15. Procédé selon la revendication 1, dans lequel la substance inorganique poreuse est choisie parmi l'aluminate-silicate de magnésium et le dioxyde de silicium.

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